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Reviewer

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

AUG 4 1977

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SUBJECT: Request for a tolerance of 1.0 ppm of  $\alpha$ -Naphthalene acetic acid (XNAA) in/on citrus fruits. DATE:

FROM: Dr. Chan, S.L.  
Toxicology Branch

*Sin-Lam Chan*  
*E for OEP 8/4/77*

TO: Mr. Fletcher, C.  
Special Registration Section

Petition No. 7E1956  
IR-4 Project  
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Recommendations:

Chemistry Branch considerations permitting, we recommend the establishment of the petitioned tolerance of 1.0 ppm of XNAA and metabolites in/on citrus fruits.

We request that a teratology study be submitted within a reasonable period of time.

A. Established and pending tolerances.

Tolerances have been established, CFR 40, 180.155 for:

- 1.0 ppm in/on apples, pears, quinces.
- 0.1 ppm in/on olives.
- 0.05 ppm in/on pineapples.

B. Referenced and related Petitions:

No new toxicological data are submitted for the current petition. The related petitions are 8E0663, 1E1094 and 1E1099. A summary of previously accepted toxicological studies is presented below:

1. Dr. Whitmore, G.E., on 8E0663 (12/22/67).

- a) 90-day rat feeding NEL = 100 mg/kg/day (XNAA).
- b) 90-day dog feeding NEL = 10 mg/kg/day (XNAA).
- c) 3-generation mouse reproduction study: no effect on reproductive performance to 600 ppm or 86 mg/kg (XNAA-O-CH<sub>3</sub>).
- d) Life-time mouse feeding: no effect on life-span to 600 ppm (XNAA-O-CH<sub>3</sub>).

2. Dr. Williams, C.H., on 1E1094 (5/19/71).

- a) Rat acute oral LD<sub>50</sub> = 1.0 gm/kg (XNAA).
- b) 2-year rat feeding NEL = 2500 ppm (XNAA-O-CH<sub>3</sub>).

3. Mr. Ritter, D.L., on 1E1099 (12/25/72).

The possible toxicity arising from the impurities and plant metabolites was cleared.

It is noted that in some studies, the methyl ester of XNAA was used instead of the salt. This is acceptable for 2 main reasons:

- a) XNAA is the principle metabolite of the methyl ester.
- b) Even though the exact amount of XNAA arising from its methyl ester is not known, the toxicity of both compounds are similarly low.

C. Studies presented (1E1099) but not previously reviewed.

1. Rat metabolism of  $\alpha$ NAA-1- $^{14}$ C, J. Agr. Food Chem., 14, 532 ('66).

Protocol: Single oral doses of 0.1, 1.0, 100 and 250 mg of  $\alpha$ NAA-1- $^{14}$ C were given to male rats. Radioactivity was monitored daily in the urine and feces and every 2 hrs. in the bile.

Results: The total radio-label excreted in 3 days was:

In urine = 71-90%  
In feces = 3-20%  
In bile = 4-21%, 2-6 hrs.

The 2 major metabolites (70-93%) in urine were naphthaceturic and naphthacetylglucosiduronic acids.

For the lower doses, the excretion in urine and feces in 24 hr. was approximately 90%.

Evaluation:  $\alpha$ NAA and metabolites are well excreted in the urine and feces.

Classification: Core minimum.

D. 1. ADI estimation.

- a) 90-day rat feeding NEL = 100 mg/kg/day.
- b) 90-day dog feeding NEL = 10 mg/kg/day.
- c) 2-year rat feeding NEL = 2500 ppm, or 125 mg/kg ( $\alpha$ NAA-O-CH<sub>3</sub>).
- d) 3-generation mouse reproduction and life time feeding NEL = 86 mg/kg ( $\alpha$ NAA-O-CH<sub>3</sub>).

Since the methyl ester of naphthalene acetic acid was used in the long-term feeding and reproductive studies and the petition is for a tolerance of the free acid, a conservative estimate of the amount of the major metabolite, the free acid ( $\alpha$ NAA) arising from the ester may be in the order of 1/10 of the parent compound. The estimated amount of  $\alpha$ NAA is then used for the calculation of the ADI which may be revised accordingly when NELs for the free acid from long-term studies should become available.

Since the 2-yr. rat feeding NEL = 125 mg/kg/day, for the methyl ester.

The projected NEL for  $\alpha$ NAA = 12.5 mg/kg/day.

Assuming then the usual factor of 100, the ADI may be estimated as:

$$ADI = 0.125 \text{ mg/kg/day.}$$

The estimated MPI for a 60 kg person is:

$$MPI = 7.50 \text{ mg/person/day.}$$

2. Exposure from established tolerances

	<u>tolerance</u> (ppm)	<u>food intake</u> (gm)	<u>exposure</u> mg/day
apples, pears, quinces	1.0	$\approx 45.0$	0.04500
olives	0.1	$\approx 2.5$	0.00025
pineapples	0.5	$\approx 5.73$	0.00030

$$\text{total exposure} = 0.0455 \text{ mg/day}$$

3. Exposure from currently petitioned tolerance.

$$\text{Exposure} = 1.0 \times 0.048 \text{ mg/person/day;}$$

$$= 0.048 \text{ mg/person/day}$$

(citrus fruits intake approximated at 48 gm per day).

4. Comparison of MPI to exposures from established and currently petitioned tolerances.

$$MPI/\text{total exposure} = 7.5/0.094$$

$$\approx 80$$

i.e. the exposure to  $\alpha$ NAA and metabolites from the established and currently petitioned tolerances is approximately 1/80 of the estimated MPI.

E. Conclusion:

Tolerances of 0.05-1.0 ppm have been established for  $\alpha$ NAA and metabolites to be in/on pineapples, olives, apples, pears and quinces. Previous and current reviews have found  $\alpha$ NAA to be of a low order of toxicity in acute, subacute and chronic studies. The MPI may be estimated from these studies to be 7.50 mg/person/day. The exposure to  $\alpha$ NAA and metabolites from the established and currently petitioned tolerances is a fraction ( $1/80$ ) of the MPI.

Subject to chemistry considerations, we recommend on the establishment of the petitioned tolerance. However, according to current requirements, a teratology study is lacking and should be submitted within a reasonable period of time.

F. References:

1. rat acute oral LD<sub>50</sub>: Toxic Substance List, 1975;
2. 90-day rat feeding: FDA files;
3. 90-day dog feeding: FDA files;
4. 3-generation mouse reproduction; and,
5. life-time mouse feeding: Finch, F., and Hartzell, A., (1945) Boyce Tomp. Inst. for Pl. Res. Vol. 14, P. 69;
6. 2-year rat feeding: FDA files.